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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/340,283	06/25/1999	ROBERT O. MESSING	GALO-007/01U	3708

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EXAMINER	
SHUKLA, RAM R	

ART UNIT	PAPER NUMBER
1632	29

DATE MAILED: 10/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/340,283	Applicant(s) MESSING ET AL.	
	Examiner Ram R. Shukla	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56-80* is/are pending in the application.

4a) Of the above claim(s) *60-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56-59 and 64-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election of the invention of group I (claims 56-59 and 64-80) in Paper No. 26 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 60-63 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 26.

3. Claims 56-59 and 64-80 are under consideration.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 56-59 and 64-80 rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure, which is not enabling. A step of comparing the binding of the test agent to or activity of PKC epsilon with other PKC isozymes is critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). It is noted that claimed invention is based on the finding of the inventors that a null mutation in PKC epsilon causing complete loss of PKC epsilon activity results in less anxiety related symptoms in a transgenic mouse. However, there are several isozymes of PKC and an inhibitor or activator that binds to one isozyme of PKC will also bind and inhibit or activate other isoforms of PKC (see figure 4b in Riovainen et al. Brain Research 624:85-93, 1993). It is emphasized that all the examples described in the specification are based on the comparison of all the results in PKC epsilon null mouse with those in a normal wild type mouse,

which clearly indicates the essentiality of the use of control in practicing the claimed invention. Therefore, use of a control PKC isozyme to differentiate between the effects of modulator on PKC epsilon or any other isozyme will be crucial to practicing the claimed invention for screening an agent that modulates the activity of PKC epsilon or binds to PKC epsilon specifically.

6. Claims 56-59 and 64-80 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for practicing the claimed methods wherein an agent is screened for specifically binding to PKC epsilon and specifically inhibiting the activity of PKC epsilon, does not reasonably provide enablement for other embodiments, for example, wherein the modulator is an activator of PKC epsilon activity and binds to PKC epsilon. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore

skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

It is noted that the claimed invention would include screening for agents that bind to and activate PKC epsilon, however, the specification does not teach as to how would an artisan use an activator of PKC epsilon as intended. It is further noted that claimed invention is based on the finding of the inventors that a null mutation in PKC epsilon causing complete loss of PKC epsilon activity results in less anxiety related symptoms in a transgenic mouse. The specification does not teach as to how an activator will be used for intended utility and an artisan would have required extensive experimentation to use an activator of PKC epsilon as intended because neither the specification nor the art at the time of the invention provided any guidance in this regard.

As noted above, the claimed invention stems from the observation that PKC epsilon null transgenic mouse had symptoms opposite to that of anxiety. This would indicate that an activation of PKC epsilon would result in an increase in the anxiety symptoms. In fact, transgenic mice expressing PKC epsilon have several phenotypes such as cardiac hypertrophy and alterations in the interaction of PKC epsilon with RACK (see Pass et al American J of Physiology (Heart Circulation Physiology) 280:H946-955, 2001; and Takeishi et al. Circulation Research 86:1218-1223, 2000). This clearly indicates that activation of PKC epsilon in a subject will not reduce anxiety rather increase anxiety. The specification does not teach how to use a modulator of PKC epsilon that does not modulate anxiety.

Next, the issue is of the specificity of the effect of the modulator on PKC epsilon since other forms of PKC have also been shown to affect anxiety. For example, a PKC gamma null mouse also exhibits antianxiety (see Bowers et al. Behavioral Genetics 30:111-121, 2000 and Bowers et al. The Journal of Neuroscience 21:RC180-185, 2001). This indicates that if an artisan was screening for agents that inhibit PKC epsilon in vitro in partially purified enzyme preparation or in a cell or in vivo, one would not know whether the effect was due to PKC epsilon or PKC gamma. In other words, if a general PKC substrate was used, an artisan would not know if the change in enzyme activity was due to PKC epsilon or

PKC gamma or any other isozyme. The specification does not provide guidance as to how to use modulators of other isozymes of PKC.

In conclusion, an artisan of skill would not have know how to use an agent which activated PKC epsilon or which modulated other isoforms of PKC and an artisan would have required extensive experimentation to use an activator of PKC epsilon as intended because neither the specification nor the art at the time of the invention provided any guidance in this regard. Therefore, limiting the scope of the claimed invention to a method wherein an agent is screened for specifically binding to PKC epsilon and specifically inhibiting the activity of PKC epsilon, is proper.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims 56-59 and 64-80 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: determining the specificity of the binding to PKC epsilon and determining the specificity of the modulation of PKC epsilon by comparing with other PKC isozymes.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the

application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

10. Claims 56-59 and 64-70 are rejected under 35 U.S.C. 102(b) as being anticipated by Hundle et al (Journal of Biological Chemistry 270:30134-30140, 1995).

Hundle et al teaches expression of PKC epsilon in PC12 cells, effect of different compounds on cells expressing PKC epsilon, purification of PKC epsilon and in vitro assays with the purified PKC epsilon (see the experimental procedures section on page 30135 and figures 1-7 and table 1). The reference also teaches effect of ethanol and nerve growth factor on PKC epsilon activity and expression. It is noted that while the cited art does not explicitly teaches a method for screening of an agent that modulates anxiety, the recited method of the instant application has only two steps, exposing the PKC epsilon to a test agent and detecting binding and both these steps are taught by the cited reference. It is further noted that since the relationship of ethanol and anxiety were well known in the art at the time of the invention, a compound that alters PKC epsilon will have anxiety modulating activity.

11. Claims 56, 58, 64, 66, 69 and 70 are rejected under 35 U.S.C. 102(e) as being anticipated by Mochly-Rosen et al (US 7,783,405, 7-21-02, effective filing date 2-1-1994).

This patent teaches inhibition of PKC epsilon activity by different inhibitors, such as PCK epsilon fragments, different chemical inhibitors of PKC epsilon such as PMA (see figures 2-7, examples 1-3). It is noted that while the cited patent does not teach that PKC epsilon inhibitors have potential anxiety modulation activity, the recited method of the instant application has only two steps, exposing the PKC epsilon to a test agent and detecting binding and both these steps are taught by the cited reference.

12. Claims 56-59 and 64-80 are rejected under 35 U.S.C. 102(b) as being anticipated by Onaivi et al (Annals of NY Acad of Sci. 844:227-224, 1998).

This art teaches effects of ibogaine on PKC isoforms, of which PKC epsilon is one of them. The art also teaches role of PKC in actions of alcohol and drug abuse. The art also teaches effects of ibogaine treatment on cocaine abuse in ICR mice in elevated maze test. Onaivi et al show that cocaine and ethanol decrease the expression of PKC epsilon in PC12 cells (see figure 4). This art also teaches PCK activity in homogenate of cells (see figure 6) and addition of PMA to the homogenate (see page 234-236). Onaivi et al also teach that if anxiety was a factor in drug dependence, ibogaine's antiaddictive property may alter CNS neurotransmission involved in anxiety. It is noted that while the cited art does not explicitly practice the method by first studying the effect of ibogaine in vitro and then in vivo, the art studies the effect of ibogaine both in an in vivo and in an in vitro settings. Furthermore, although the art does not explicitly teach an in vitro method for screening of an agent that modulates anxiety, the recited method of the instant application has only two steps, exposing the PKC epsilon to a test agent and detecting binding and both these steps are taught by the cited reference. It is further noted that since the relationship of ethanol and anxiety were well known in the art at the time of the invention, a compound that alters PKC epsilon will have anxiety modulating activity as is the case with ibogaine.

No claim is allowed.

When amending claims, applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c). For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Applicants are also requested to submit a copy of all the pending/under consideration claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Dianiece Jacobs whose telephone number is (703) 305-3388.

Ram R. Shukla, Ph.D.

RAM R. SHUKLA
PATENT EXAMINER

RAM R. SHUKLA, PH.D
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